example, in Example 4, pages 14-15, and Table 5. Applicants respectfully request the entry of these amendments and new claims.

The Office withdrew claims 21-28 from consideration as directed to non-elected inventions, but noted that "[u]pon allowability, process claims which depend from or otherwise include all the limitations of the allowable product will be rejoined as appropriate." (Office Action at page 2.) The withdrawn claims correspond to claims 21-22, 25-28, and 32-40 in the application as amended.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

The Office rejected claims 11-20 as allegedly indefinite. First, the Office contended that claim 11 is confusing as worded. Applicants have amended claim 11 to replace the phrase "in which" with "comprising." This change was made solely to provide further clarity without narrowing the scope of the claims. Applicants submit that claim 11 is definite because "(S)-hydroxynitrile lyase immobilized on a carrier" is a type of "immobilized enzyme."

The Office next contended that claims 14-15 and 19-20 are confusing due to the recitation of "*Poaceae (Gramineae)*." However, Applicants have attached evidence showing that this is, in fact, a known way to describe this family of grasses. The abstract by Grote et al. (*J. Allergy Clin. Immunol.*, 108(1):109-15 (2001); Exhibit A, attached) uses this exact nomenclature. Moreover, the attached taxonomy search from the National Library of Medicine Internet database explains that *Poaceae* and *Gramineae* are synonyms. (Exhibit B, attached.) Thus, this term is definite and Applicants request that this rejection be withdrawn.

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The Office also rejected claims 13-14 and 19-20, asserting that they are in improper form under M.P.E.P. § 608.01(n). Applicants note that claim 20 is not a multiple dependent claim, but have amended claims 13, 18, and 21 to recite either "claim 11 or 12" or "claim 16 or 17," rendering this rejection moot. However, Applicants nevertheless submit that "one of claims 11 and 12" has exactly the same meaning as "claim 11 or 12." In fact, one of the M.P.E.P. § 608.01(n) "acceptable multiple dependent claim wording" examples is nearly identically worded to Applicants original claims and recites a claim dependent on "one of claims 4-7."

The Office rejected claim 17 for the recitation of "the" rather than "a" or "an." Applicants have amended claim 17 for consistency with claim 12, but note that the use of a definite article instead of an indefinite article does not change the meaning of the term it modifies.

Finally, the Office rejected claims 12 and 17 because they do not contain the words "the group consisting of" following the phrase "selected from." Applicants point out, however, that M.P.E.P. § 2173.03(h)(I) does not require any particular phraseology. Instead, it points out that, in general, "[a]lternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims." *Id.* Moreover, support for the "X is selected from A, B, and C" language may be found in several places, such as Annex B, Parts 1 and 2 (PCT) of the M.P.E.P. (specifically, Example 20, pages AI-61 to AI-62 of the August, 2001, edition), and in the Training Materials for Examining Patent Applications with Respect to 35 U.S.C. § 112, First Paragraph - Enablement of Chemical/Biotechnical Applications, released August, 1996, (specifically, Examples H and J). These examples make it clear that the phrase

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"X is selected from A, B, and C" is proper claim language. Therefore, Applicants request that this rejection be withdrawn.

Rejection of claims 11-13 and 16-18 under 35 U.S.C. § 102(b) over Wehtje et al. (1988) ("Wehtje 1988")

The Office contended that Wehtje 1988 (*Appl. Microbiol. Biotechnol.*, 29: 419-25 (1988)) "teaches an (S)-hydroxynitrile lyase which is immobilized on a carrier comprising a porous inorganic material," and that "the mean pore diameter is 200 Å." (Office Action at page 4.) Based on these contentions, the Office concluded that Wehtje 1988 anticipates claims 11-13 and 16-18. Applicants respectfully traverse this rejection.

Applicants note that claim 11 is amended to recite an "immobilized enzyme comprising (S)-hydroxynitrile lyase derived from one or more of *Euphorbiaceae*, *Poaceae(Gramineae)*, and *Olacaceae* absorbed on a carrier comprising a porous inorganic material."

The Wehtje 1988 disclosure cannot anticipate the claimed invention for several reasons. Most importantly, Wehtje 1988 describes not an (S)-hydroxynitrile lyase, as required by claims 11-13 and 16-18, but a mandelonitrile lyase, also known as (R)-hydroxynitrile lyase. (Wehtje 1988, Summary; *see also* Hughes et al., *Arch. Biochem. Biophys.*, 311(2): 496-502 (1994) and Wajant et al., *Plant Sci.*, 108: 1-11 (1995).) These are unrelated proteins with different physical and chemical properties. For example, (S)-hydroxynitrile lyase from *Manihot* is a homotetramer of 33 kilodalton subunits, while mandelonitrile lyase from *Prunus amigdalus*, as described in Wehtje 1988, is a 60 kilodalton monomer. (Wajant et al. (1995), Abstract and Table 5; compare the *Rosaceae* and *Euphorbiaceae* columns, for example.) The reactions they catalyze

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yield products with different stereochemistry. (Hughes et al. at page 496, col. 2.) Mandelonitrile lyase requires a flavin adenine dinucleotide (FAD) cofactor, while (S)-hydroxynitrile lyases generally do not. (Wajant et al. (1995) at Table 5.) The two protein groups do not share any significant sequence homology (Hughes et al. at page 501-2, Discussion, first paragraph.) Their respective isoelectric points also differ. For example, that of *Manihot* (S)-hydroxynitrile lyase is about 4.1 to 4.6, while that of *Prunus amigdalus* mandelonitrile lyase is about 5.0. (Hughes et al. at page 499; Seely et al., *J. Mol. Biol.*, 241(19): 4457-62 (1966).) Thus, Wehtje 1988 cannot anticipate claims 11-13 and 16-18 simply because it refers to a different protein than that of these claims.

Second, Wehtje 1988 describes mandelonitrile lyase from the almond (*Prunus amygdalus*), which does not fall within the *Euphorbiaceae, Poaceae(Gramineae)*, or *Olacaceae*. Finally, even if, *arguendo*, the two proteins were the same, Wehtje 1988 describes covalently coupling mandelonitrile lyase to the support, while claim 11 recites "(S)-hydroxynitrile lyase absorbed on a carrier." (Wehtje 1988, Summary, first sentence; page 421 "Enzyme immobilization" section and Table 1.) For all of the above reasons, Wehtje 1988 cannot anticipate claims 11-13 and 16-18 and Applicants respectfully request the withdrawal of this rejection.

Rejection of claims 11, 12, 16, and 17 under 35 U.S.C. § 102(b) over Wehtje et al. (1990) ("Wehtje 1990") or Wehtje et al. 1993 ("Wehtje 1993")

The Office also contended that Wehtje 1990 (*Biotechnol. Eng.*, 36: 39-46 (1990)) or Wehtje 1993 (*Biotechnol. Eng.*, 41: 171-8 (1993)) anticipate claims 11, 12, 16, and 17, and that these articles also refer to "an (S)-hydroxynitrile lyase which is immobilized on a carrier comprising a porous inorganic material." (Office Action at page 4.)

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Applicants traverse this rejection because, like Wehtje 1988, neither of these articles refers to (S)-hydroxynitrile lyase. Instead, they refer to mandelonitrile lyase ((R)-hydroxynitrile lyase) and other, unrelated enzymes, such as α-chymotrypsin. (See the Abstract and Introduction of Wehtje 1990 and the Materials and Methods section of Wehtje 1993.) Because (S)-hydroxynitrile lyase is not mentioned in either of these articles, neither can anticipate claims 11, 12, 16, and 17, which recite "an immobilized enzyme comprising (S)-hydroxynitrile lyase." Applicants respectfully request the withdrawal of this rejection.

Rejection of claims 11-20 under 35 U.S.C. § 103(a)

The Office contended that claims 11-20 are obvious over Wehtje 1988, taken with Wehtje 1990 and Wehtje 1993, and also with Effenburger et al. (U.S. Patent No. 5,885,809; "Effenburger") and Andruski et al. (U.S. Patent No. 5,177,242; "Andruski"). (Office Action at pages 4-5.) Applicants respectfully traverse this rejection.

The Office asserted that the three Wehtje articles disclose immobilization of (S)-hydroxynitrile lyase on a carrier comprising a porous inorganic material. The Office then relied on Effenburger and Andruski for a disclosure that *Hevea*, *Manihot*, and *Sorghum* can produce (S)-hydroxynitrile lyase, thus concluding that it would have been obvious for one of ordinary skill in the art to modify the teachings of the Wehtje articles by using a protein from one of these other sources.

However, as explained in the previous two sections, the Wehtje articles, in fact, do not discuss (S)-hydroxynitrile lyase, but mandelonitrile lyase ((R)-hydroxynitrile lyase), a protein with a different structure, oligomerization state, stereospecificity,

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cofactor requirement, and isoelectric point. Because of the differences between the mandelonitrile lyase of Wehtje and the present (S)-hydroxynitrile lyases, the ability to absorb the claimed (S)-hydroxynitrile lyases on a "carrier comprising a porous inorganic material" could not be reasonably predicted from the disclosures of the three Wehtje articles.

As an illustration of this point, Wehtje 1993 states that "[a]dsorption of proteins onto surfaces [is] known to involve some degree of conformational changes in the protein molecule. Hydrophobic interactions within the protein structure are important for the overall stability of the protein molecule. Upon adsorption these hydrophobic interactions may be disturbed and hydrophobic parts may instead interact with the support, with a subsequent change in the protein structure." (Wehtje 1993 at page 177, col. 1, last full paragraph, citations omitted.) The article goes on to state that such findings, resulting in enzyme deactivation have been observed. (*Id.*)

Effenburger and Altshuler do not remedy the deficiency of the three Wehtje articles. While Effenburger does discuss (S)-hydroxynitrile lyase, it provides no disclosure of its absorption to any "carrier comprising a porous inorganic material." Instead, it discusses the use of nitrocellulose, an organic material. (Effenburger at col. 3, lines 40-52) Applicants point out that nitrocellulose is disadvantageous because it has a low absorption ratio for this enzyme. (Specification at page 1, lines 9-20.)

Altshuler discusses covalent chemical attachment of (S)-hydroxynitrile lyase to a material, not absorption of the enzyme. For example, the method of Altshuler involves treating the material with PEI, then with glutaraldehyde, to which the protein will covalently bind. (Altshuler provides a general discussion of this process at col. 2, lines

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5-16 and 30-35; col. 3, lines 55-61; and col. 4, line 66, to col. 5, line 8. It provides more detailed description at col. 5, line 58, to col. 6, line 49; and in Example 1, part A, at col. 6-7.) This glutaraldehyde covalent attachment is similar to that discussed in Wehtje 1988. (Wehtje 1988 at page 420, col. 2, and Table 1.) Therefore, Altshuler's teachings do not suggest absorbing the protein on a "carrier comprising a porous inorganic material."

As a whole, Applicants submit that the combination of these five publications does not provide a motivation for one of ordinary skill in the art to absorb the claimed (S)-hydroxynitrile lyases on the claimed carriers comprising a porous inorganic material. Nor does the combination provide any reasonable expectation of success in doing so. One could not reasonably predict the behavior of an (S)-hydroxynitrile lyase when absorbed on the claimed carriers based on the disclosures of Wehtje because the absorption efficiency and the effects of the absorption on conformation and enzyme activity are expected to be different between the (R) and (S)-hydroxynitrile lyases due to their different structures and chemical properties. (See Wehtje 1993 at page 177, second full paragraph.) Effenburger and Altshuler do not remedy this deficiency because they describe materials and methods that are quite different from those of the instant claims. Thus, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: August 23, 2002

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APPENDIX TO AMENDMENT OF AUGUST 23, 2002

Version with Markings to Show Changes Made

Amendments to the Claims

11. An immobilized enzyme [in which] comprising (S)-hydroxynitrile lyase derived from one or more of *Euphorbiaceae*, *Poaceae* (*Gramineae*), and *Olacaceae* [is immobilized in] absorbed on a carrier comprising a porous inorganic material.

13. The immobilized enzyme according to [one of claims 11 and 12] claim 11 or 12, wherein said carrier comprising a porous inorganic material has a pore size of 10-80 nm.

16. A method for producing an immobilized enzyme, comprising [immobilizing] absorbing (S)-hydroxynitrile lyase derived from one or more of *Euphorbiaceae*, *Poaceae* (*Gramineae*), and *Olacaceae* [in] on a carrier comprising a porous inorganic material.

17. The method for producing an immobilized enzyme according to claim 16, wherein said carrier comprising a porous inorganic material is selected from [the sintered clay carrier, the silica carrier, the alumina carrier and the silica alumina carrier] a sintered clay carrier, a silica carrier, an alumina carrier and a silica alumina carrier.

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18. The method for producing an immobilized enzyme according to [one of claims 16 and 17] claim 16 or 17, wherein said carrier comprising a porous inorganic material has a pore size of 10-80 nm.

21. A method for producing optically active cyanohydrin, comprising bringing the immobilized enzyme according to [one of claims 11 and 12] claim 11 or 12 into contact with a carbonyl compound and a cyanogen compound in the presence of a slightly water-soluble or water-insoluble organic solvent.

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